PROTOCOL

FULL TITLE	A randomised controlled trial to assess the pharmacokinetics and pharmacodynamics of intramuscular, intravenous and oral administration of tranexamic acid in women giving birth by caesarean section
SHORT TITLE	Pharmacokinetics and pharmacodynamics of tranexamic acid in women having caesarean section birth
ACRONYM	WOMAN-PharmacoTXA

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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i. LIST OF CONTENTS

ii LIST OF ABBREVIATIONS

AE	Adverse Event
APH	Antepartum Haemorrhage
AR	Adverse Reaction
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Chief Investigator
CI	Confidence Interval
Cmax	Maximum Concentration
COV	Covariate
CS	Caesarean Section
CT	Computerized Tomography
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EMA	European Medical Agency
FBC	Full Blood Count
g	Gram
GCP	Good Clinical Practice
h	Hour
IB	Investigator Brochure
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice
IM	Intramuscular
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IV	Intravenous
L	Litre
LMICS	Low and Middle-Income Countries
LSHTM	London School of Hygiene & Tropical Medicine
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare Products Regulatory Agency
min	Minute
mg	Milligram
mL	Millilitre

μL	Microlitre
PAI	Plasminogen Activator Inhibitor
PD	Pharmacodynamics
PFIM	Population Fisher Information Matrix
PI	Principal Investigator
PK	Pharmacokinetics
PO	Orally
PPH	Post-Partum Haemorrhage
PWR	Power
QP	Qualified Pharmacist
RCT	Randomised Control Trial
REC	Research Ethics Committee
RR	Relative Risk
SAE	Serious Adverse Event
SAEM	Stochastic Approximation Expectation Maximization
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAFI	Thrombin Activatable Fibrinolytic Inhibitor
tPA	Tissue Plasminogen Activator
TXA	Tranexamic Acid
WHO	World Health Organisation

iii. TRIAL SUMMARY

Trial Title	A randomised controlled trial to assess the pharmacokinetics and pharmacodynamics of intramuscular, intravenous and oral administration of tranexamic acid in women giving birth by caesarean section	
Acronym	WOMAN-PharmacoTXA	
Clinical Phase	Phase 2 - Exploratory study	
Trial Design	Prospective, randomised, open-label	
Trial Participants	Women undergoing caesarean section (CS) with at least one known risk factor for PPH	
Planned Sample Size	120 women: 30 receiving oral liquid, 30 receiving intramuscular, 30 receiving intravenous and 30 receiving no tranexamic acid (TXA) who have at least 6 post treatment evaluable PK samples.	
Treatment duration	Once only administration of 1 gram of TXA either intramuscularly or intravenously, or 4 grams oral liquid or none.	
Follow up duration	7 days	
Planned start date	1 May 2020, or when the first evaluable participant has been recruited.	
Planned end date	1 May 2021, or when 120 evaluable participants have been recruited.	
Primary	**Objectives**	**Outcome Measures**
	Pharmacokinetic parameters in mothers	Blood TXA over time up to 24 hours after randomisation
Secondary	1. Placenta transfer of TXA 2. Pharmacodynamic parameters in mothers 3. Blood loss at 2 hours from CS 4. Adverse events in mother and neonate 5. Clinical diagnosis of primary postpartum haemorrhage (PPH)	1. Concentrations of TXA in cord blood after birth and neonate level within the first 24 hours of birth 2. D-dimer concentrations over time up to 24 hours after randomisation 3. Volume of blood lost from incision to 2 hours from CS 4. Local reactions at injection site and adverse events up to 7 days 5. Clinical diagnosis of PPH up to 24 hours after birth (total blood loss of >1000 mL or any blood loss sufficient to cause haemodynamic instability or requires treatment)

Investigational Medicinal Product(s)	Tranexamic acid (intravenous, intramuscular and oral liquid)
Formulation, Dose, Route of Administration	Women will be randomised to receive one of the following treatments. Additionally, women will receive all standard care for the active management of 3rd stage of labour: • Tranexamic acid (100 mg/mL) 1 gram by intravenous injection • Tranexamic acid (100 mg/mL) 1 gram divided in 2 x 0.5 g/5 mL injections by intramuscular injections • Tranexamic acid (1 g/10 mL) 4 grams by oral solution • No tranexamic acid

iv. TRIAL OVERVIEW

WOMAN-PharmacoTXA
TRIAL OVERVIEW FLOW CHART

Initial Screening
- Women in hospital giving birth by CS
- History of at least one risk factor for PPH
- Adult (≥18 years old)
- No history of renal impairment

↓

Obtain informed consent

↓

Screening for eligibility and baseline data collection:
- Demographic and anthropometric data: ethnicity, age, height and weight
- Medical history and risk factors for PPH
- Reason for Caesarean Section birth
- Vital signs: blood pressure, temperature, heart rate, and respiratory rate
- Collection of blood sample for PK analysis and clinical blood tests to assess full blood count, renal function and D-dimer for PD analysis.
- Foetal status

↓

Randomise:
Women will be allocated to one of the following treatments after enrolment and about ONE hour prior to caesarean section in addition to standard care:
- Intravenous TXA (1g, total volume 10mL)
- Intramuscular TXA (1g divided in two 0.5 g/5 mL injections)
- Oral solution TXA (4g, total volume 40mL)
- No TXA

↓

TREATMENT
Timepoint T_0 – Give intervention as randomised about 1 hour (± 30 min) prior to caesarean section.

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Follow up data: Collection blood samples after TXA administration, check injection sites, check vital signs. Do not miss a time point. If delayed due to clinical reasons, collect as soon as possible and record time.

Maternal blood samples	Placenta cord and Neonate blood samples
$T_1 = T_0 + 15$ min (± 5 min)	Umbilical cord sample: When the umbilical cord is clamped.
$T_2 = T_0 + 30$ min (± 15 min)	Neonate sample: when routine heel prick tests is done
$T_3 = T_0 + 1$h (± 30 min)	
$T_4 = T_0 + 2$h (± 1h)	
$T_5 = T_0 + 4$h (± 1h)*	
$T_6 = T_0 + 8$h (±1h)*	
$T_7 = T_0 + 12$h (±2h)*	
$T_8 = T_0 + 24$h (±2h)**	

If (in exceptional circumstances) a sample cannot be taken at the optimal stated time, the sample should be taken 15 minutes before the next sample (which can be delayed by 15 minutes if needed) so that every patient has a total of six post TXA samples.
- **** sample for D-Dimer also***
- ***** Repeat D-dimer, routine FBC and renal function (or at discharge if before 24 hours)***

↓

Follow-Up data (up to discharge, death or day 7 whichever is earliest):
- Local reactions at injection sites
- Prespecified Adverse Events: Nausea, vomiting, diarrhoea, thromboembolic events and seizures
- Vital signs: temperature, blood pressure, heart rate and respiratory rate
- Concomitant treatments (including IV fluids and blood products from T_1 to T_8)
- Measured blood loss from the onset of surgery and within first 2 hours after CS
- Clinical diagnosis of PPH
- Interventions for preventing and treatment of PPH
- Adverse Events in mother and baby(ies)
- Neonate status

1 BACKGROUND

1.1 Summary

Postpartum haemorrhage (PPH) is a leading cause of maternal mortality and morbidity. About 6% to 10% of all women giving birth develop PPH and it accounts for around 100,000 maternal deaths every year.[1-3] Ninety-nine percent of deaths from PPH are in low and middle-income countries (LMICs).[4] Many women who survive experience severe morbidity. Some women need surgery to control the bleeding (e.g. exploratory laparotomy, uterine artery ligation, brace sutures) and many require a hysterectomy, thus removing the possibility of having more children.

Tranexamic acid (TXA) is a synthetic analogue of the amino acid lysine, which inhibits fibrinolysis by blocking the lysine binding sites on plasminogen. TXA reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots (fibrinolysis).[5] Plasminogen produced by the liver is converted into the fibrinolytic enzyme plasmin by the tissue plasminogen activator (tPA). Plasminogen and tPA bind to lysine residues on fibrin leading to localised plasmin formation and fibrin cleavage.[6] TXA is a molecular analogue of lysine that inhibits fibrinolysis by competing with fibrin for the lysine binding sites in plasminogen. TXA inhibits the capacity of plasminogen and plasmin to bind to fibrin, hence preserving blood clots from plasmin-mediated lysis.[5]

TXA reduces surgical bleeding and death due to bleeding in trauma patients. The WOMAN trial assessed the effects of intravenous TXA in 20,060 women with PPH.[7] TXA significantly reduced death due to bleeding with no adverse effects. When given within three hours of birth, TXA reduced death due to bleeding by nearly one-third (relative risk (RR)=0.69, 95% CI 0.52 to 0.91; p=0.008). However, for many women, treatment is too late to prevent death from PPH. Most PPH deaths occur in the first hours after giving birth.

Every fifteen minutes treatment delay reduces the survival benefit by about 10% until around three hours after which there is no benefit.[8] One of the main barriers to rapid treatment is the need for an intravenous (IV) injection. Medical personnel who are trained to insert intravenous lines are not always available in rural areas or when the emergency occurs far from a clinic or a hospital. Although TXA is available for oral (tablet or oral solution) and intravenous use, there has been little research into different routes of administration. Intramuscular injection would be easier and faster to administer and would require less training than IV use, and the use of the oral solution as opposed to tablets may reduce the time needed to reach therapeutic levels.

Given the importance of rapid administration and the good safety profile TXA could be given prophylactically before childbirth. However, the pharmacokinetic properties of TXA in pregnant women have not yet been established.

Studies in healthy volunteers show that therapeutic plasma TXA levels (plasma TXA >10 mg/L)[9] are reached rapidly (within 30 min) after IM injection.[10,11] Pharmacokinetic modelling of the administration of 4 g of TXA resulted in a plasma concentration of 10 mg/L within 15 min (data on file) If absorption was similarly rapid in pregnant women, this would strongly suggest the IM and oral routes as potential alternatives to IV use.

Currently, the Trauma-INTACT trial (ClinicalTrials.gov: NCT03875937) is assessing the PK of TXA administered intramuscularly in bleeding trauma patients, and the PharmacoTXA trial (ClinicalTrials.gov: NCT03777488) is assessing the PK of TXA administered intramuscularly or orally in healthy volunteers. An ongoing RCT called TRACES (TRAnexamic Acid to Reduce Blood Loss in Hemorrhagic CESarean Delivery) aims to assess the pharmacokinetics and pharmacodynamics effects of two doses of TXA (0.5 and 1 g) injected intravenously in women with an ongoing PPH after delivery.[12]

Pregnancy induces physiologic changes and adaptations in many organ systems, e.g. increased fat and total body water, increased maternal blood volume, cardiac output, decreased blood pressure, delayed gastric emptying.[13] These and other physiologic changes may alter the pharmacokinetic properties of medicines, i.e. their distribution, absorption, metabolism and excretion. This, in turn, could impact the pharmacodynamic properties of medicines, i.e. their effects on the body. The physiology of birth, possible trauma, blood loss and the treatments for blood loss such as transfusions, could also affect, the pharmacokinetic and pharmacodynamics properties of a drug.

PPH can occur without warning in most women. However, some risk factors are known to be associated with an increased risk of PPH. Factors known to increase the risk of PPH prior to giving birth include those listed as follows:[14,15]

- parity >3
- increased maternal age (≥ 35 years)
- anaemia (≤ 9 g/dL)
- multiple gestation
- foetal macrosomia
- intra-amniotic infection, e.g. prolonged rupture of membranes
- prolonged labour (more than 12 hours)
- fibroids
- placenta abruption

- placenta praevia
- placenta accreta
- uterine anomalies
- previous PPH
- polyhydramnios
- pre-eclampsia with thrombocytopenia e.g. haemolysis, elevated liver enzymes and low platelet count (HELLP)
- gestational hypertensive disorder of pregnancy
- dead foetus in utero
- obesity (BMI (body mass index) of more than 35)
- gestational diabetes

In this study we will assess the pharmacokinetics (PK), pharmacodynamics (PD), safety and efficacy of TXA administered by intravenous, intramuscular or oral routes in women giving birth by C-section (CS) with at least one risk factor for PPH. Where women are randomised to receive TXA, it will be administered 1 h before CS, and they will be given 1 g IV or IM TXA or a 4 g PO. Blood samples will be taken from the women at different time points from immediately before the administration of TXA (1 h before CS) to 24 h after receipt of intervention. Blood samples from the umbilical cord after clamping and from neonates (obtained from the sample taken for routine heel prick test) will be taken to measure the amount of TXA transferred from the mother to the neonate via the placenta. The efficacy of the different routes of TXA administration in preventing blood loss, reducing fibrinolytic activity, and the safety of the interventions will be evaluated.

1.2 Existing knowledge relating to the condition under investigation

Pregnancy is characterised by increased coagulability and decreased fibrinolysis to allow the woman's body to respond and control bleeding resulting from placental separation. Hypofibrinolysis during pregnancy is the result of higher levels of plasminogen activator inhibitor-1 and -2 (PAI-1 and PAI-2)[16,17] and some studies report increased levels of the thrombin activatable fibrinolytic inhibitor (TAFI).[16] Despite the hypofibrinolytic state, D-dimer levels increase up to four-fold by the time of delivery[17-19] revealing that fibrinolysis is active. Indeed, during pregnancy levels of tPA are also increased.[16] One retrospective study on 1,032 women who had blood parameters checked during pregnancy showed that women who had PPH had higher D-dimer levels (≥ 2.7 μg/mL) during the early third trimester (gestational week 35-37) compared to women who did not have PPH.[20] The level of D-dimer in women giving birth vaginally or by CS was not different at term (≥ 37 weeks gestation)[21] and on the day of delivery.[21,22]

Generally, D-dimer levels are further increased within the first 2 h post-partum whatever the mode of delivery, vaginal or by CS.[21] In addition, there is a significant increase in tPA activity and tPA antigen and a decrease in PAI activity, in the immediate post-delivery period. The changes in t-PA and PAI-1 observed after Caesarean section are not significantly different from those observed after normal vaginal delivery.[23]

In complicated pregnancies fibrinolysis parameters can differ from normal pregnancies. For instance, in severe pre-eclampsia, or early-onset pre-eclampsia, the mean D-dimer levels are significantly higher than D-dimer levels during the third trimester in normal pregnancies.[19] Higher D-dimer levels in pre-eclampsia cases are likely due to lower levels of PAI-2.[16]

Because of the active fibrinolysis in pregnant women, TXA may have a beneficial role in preventing PPH (see section 1.3, "Prevention of postpartum haemorrhage").

Results from clinical trials of TXA in elective surgery show that when TXA is given before and during the surgical procedure it reduces blood loss by about one third.[24] As the participants in this trial are experiencing surgery and have a history with at least one risk factor for PPH, they have the potential to benefit from a reduction of blood loss.

1.3 Summary of relevant pre-clinical and clinical trials

Although the pharmacokinetics of TXA after IV administration has been well studied, there have been fewer studies of IM use and the oral use of the liquid form of TXA.

Oral administration of TXA in the tablet form: This mode of administration has been well studied and is licenced for use for the treatment of menorrhagia.[25-27] Pharmacokinetic studies showed that it takes about 2.5 h for TXA to reach a plasma concentration >10 mg/L after the oral administration of 1.3 g of TXA (tablets).[25-27] The oral administration of doses of TXA ranging from 500 to 2000 mg confirmed the time needed to reach the maximum concentration (Cmax) relative to dose used.[11,28,29] Due to the time taken to achieve blood levels needed to inhibit fibrinolysis using oral TXA tablets, its use in the treatment of PPH is limited.

Oral liquid administration: Pharmacokinetic modelling of the administration of 4 g of TXA resulted in a plasma concentration of 10 mg/L (which would result in inhibition of fibrinolysis[9]) within 15 min, and a Cmax above 30 mg/L after about 2 h (data on file).

Intramuscular TXA administration: A systematic review identified two pharmacokinetic studies of TXA administered by IM injection in healthy volunteers.[10,11] These showed that the bioavailability of TXA after IM injection is over 95% with therapeutic TXA levels (>10 mg/L) achieved within about 30 minutes

from the administration. There were no adverse effects. The meta-analysis and pharmacokinetic modelling based on data from these studied showed that TXA therapeutic levels would be reached in less than 30 min in both healthy volunteers and trauma patients.[30] Nevertheless, larger studies are needed in patient populations before IM TXA can be recommended as an alternative to IV use. Preliminary data from the Trauma-INTACT trial on the IM administration of 1 g of TXA in 16 out of a planned sample of 30 bleeding trauma patients show that the serum concentration of TXA reached a concentration of about 15 mg/L 15 min after the IM injection and a Cmax of about 20 mg/L after about 45 min (data on file).

We will study the pharmacokinetics and pharmacodynamics of TXA after IV or IM injection, or oral liquid administration.

TXA has been used to prevent and treat bleeding for over 40 years. The clinical evidence is summarised below:

Obstetric haemorrhage:

Treatment of postpartum haemorrhage: A systematic review identified two trials involving 20,212 women and showed that 1 gram of IV TXA (plus an additional 1 gram if bleeding continued up to 24 hours) reduces the risk of death due to bleeding after PPH compared to placebo. There was no evidence of any increase in thromboembolic events, seizures or other side effects with TXA.[31] Based on this evidence, the WHO recommends the early use of IV TXA (within 3 hours of birth) in women with PPH.[32] The WHO also states that "research on other routes of TXA administration is a priority." A high dose of TXA (4 g IV followed by 1 g over 6 hours) inhibits the level of D-dimer in women with PPH. However, the high dose caused side effects including nausea and vomiting and visual disturbance.[33]

Prevention of postpartum haemorrhage:

The randomised, double-blind placebo-controlled TRAAP trial examined the use of TXA to prevent PPH. It enrolled 4,079 women who were giving birth vaginally in French hospitals.[34] Of these 4,079 women, 3,891 were included in a modified intention-to-treat population. PPH (defined as blood loss of ≥500 mL as measured in a collector bag) occurred in 156 women (8.1%) in the TXA group and in 188 women (9.8%) in the placebo group (RR=0.83, 95% CI=0.68-1.01, p=0.07). Blood loss >500 mL as measured in the collector bag and clinically-significant PPH according to caregivers were both reduced in the TXA group (respectively 6.6% versus 8.8%, P=0.01, and 7.8% versus 10.4%, p=0.004). The need for additional uterotonics was also reduced (7.3% versus 9.7%, p=0.003). Nausea or vomiting in labour wards were more common in the TXA group (7.0% versus 3.2%, p<0.001), but the risk of vascular occlusive events in the 3 months after delivery did not differ from placebo. No significant differences

were found for thrombotic events or other adverse outcomes. Pre-specified subgroup analyses found that TXA reduced the PPH in women who had instrumental delivery (9.4% versus 14.7%, RR=0.64, 95% CI=0.42-0.98; p=0.04) but not in those with spontaneous delivery, and in women with episiotomy (12.6% versus 17.3%, RR=0.73, 95% CI=0.53-1.00; p=0.049), but not in those without episiotomy.

A systematic review on TXA use to prevent PPH in women giving birth vaginally or by CS and including 26 randomised trials found that most trials were small and unreliable.[35] Another systematic review evaluated the effectiveness and safety of prophylactic TXA in preventing PPH compared to placebo or no treatment.[36] This review included 12 studies, 9 trials on women undergoing elective CS (2,453 participants) and 3 trials involving women giving birth vaginally (832 participants). Women undergoing CS received TXA 10-20 minutes before skin incision. TXA had a positive effect on both blood loss >400 or >500 mL (RR=0.55, 95% CI=0.44-0.69, three trials, 566 participants) and >1000 mL (RR=0.43, 95% CI=0.23-0.78, four trials, 1534 participants). In women who gave birth vaginally, TXA had a positive effect for blood loss >400 or >500 mL (RR=0.42, 95% CI=0.28-0.63, three trials, 832 women), but not for blood losses >1000 mL (RR=0.28, 95% CI=0.06-1.36, two trials, 559 women). There was no difference between women who received TXA versus placebo or no interventions in the number of thromboembolic events. Women who received TXA versus placebo or no intervention developed side effects (average RR=2.48, 95% CI=1.36-4.50, eight trials, 2,616 participants) such as nausea, vomiting, diarrhoea, or headache.[36]

A systematic review including 18 studies (comprising 1,764 women receiving TXA and 1,793 controls in total) on the prophylactic intravenous administration of TXA to prevent PPH following a CS found that TXA had a beneficial effect on reducing blood loss for PPH >400 mL (RR=0.40, 95% CI= 0.24-0.65, p=0.0003, five trials, 786 participants), severe PPH >1000 mL (RR=0.32, 95% CI= 0.12-0.84, p=0.02, five trials, 1,850 participants) and the need for red blood cells transfusion (RR=0.30, 95% CI=0.18-0.49, p=0.00001).[37] Only one study reported cases of deep vein thrombosis (2 in TXA-treated women and 2 in controls), whereas no severe adverse events were reported by the other 17 studies. It should be noted that nine studies were open label, thus being at risk of performance bias. Moreover, there was substantial heterogeneity across studies due to study design differences, e.g. PPH definition and blood loss assessment. The included studies did not evaluate the effect of TXA on maternal death probably because of the small enrolled population sizes.[37] This review did not evaluate the efficacy of TXA in preventing PPH after vaginal delivery because the authors found only two RCTs addressing this case.

A systematic review on the prophylactic use of TXA in cases of elective CS or abdominal myomectomy included 16 trials. Of the 2,949 total women included, 2,789 underwent CS.[38] In CS cases, the prophylactic use of TXA reduced blood loss >500 mL (3 studies, 374 participants, RR=0.52, 95%

CI=0.35-0.77), blood loss >1000 mL (3 studies, 1,524 participants, RR=0.38, 95% CI=0.18-0.81), and blood transfusion (4 studies, 968 participants, RR=0.32, 95% CI=0.17-0.59). Some of the trials included in the reviews by Novikova et al.,[36] Franchini et al.,[37] and Topsoee et al.[38] were considered to be too small or unreliable in the more thorough review conducted by Ker et al.[35] Thus, even though TXA appears to be a promising drug to prevent PPH, adequately powered studies are needed to support its widespread use. At present, a large international RCT studying the effect of TXA on preventing PPH in women with anaemia who will give birth vaginally is under way.[39] TXA is administered intravenously immediately after the clamping/cut of the umbilical cord. This trial will recruit 10,000 women and in addition to the effect on PPH, it will evaluate the effect of TXA on a number of health outcomes such as haemoglobin level, quality of life, organ dysfunction, sepsis, adverse events and death.[39]

Antepartum haemorrhage

Antepartum haemorrhage (APH) occurs after 24 weeks of pregnancy. A systematic review on the use of TXA during pregnancy and in postpartum reported the findings from four observational studies.[40] These studies included a total of 343 women who developed APH because of placental abruption (259 women), placenta praevia (71) and bleeding of unknown cause (13). Among these 343 women, 268 received 3 g of TXA orally for more than 3 days, and 6 received 4 g of TXA orally for 1-12 weeks. One study reported giving 1 g of TXA intravenously during the acute phase of the APH to 73 women. None of the 343 women developed bleeding diathesis. Only one study reported adverse events, with two women developing pulmonary embolism (one woman received 3 g of TXA for 61 days, and the other received 4 g for 15 days). No adverse events on neonates due to TXA were reported.[40] TXA was effective in arresting bleeding in women with early-pregnancy bleeding.[41]

Traumatic haemorrhage

The CRASH-2 trial involving 20,211 trauma patients found that early administration of TXA reduces death due to bleeding by about one third. There was no evidence for an increase in risk of thromboembolic events, seizures or any other side effects associated with TXA.[42]

Surgical haemorrhage

A systematic review of 129 randomised trials found that TXA reduced the risk of receiving a blood transfusion by 38% and the amount of blood loss by 34% in patients undergoing surgery. The effect of TXA on risk of thromboembolic events was uncertain.[43]

Intracranial haemorrhage

Spontaneous intracerebral haemorrhage: A systematic review including nine randomised controlled trials suggest that TXA reduces re-bleeding. However, long term use of TXA may increase the risk of cerebral ischaemia in these patients. There is some evidence that shorter treatment might reduce re-bleeding without an increase in the risk of ischaemia.[44]

A trial of TXA in patients with spontaneous intracerebral haemorrhage found no statistically significant differences in functional status or death at day 90. There were fewer deaths at day 7 in the TXA group.[45]

Traumatic brain injury: The results of two randomised trials in patients with traumatic brain injury showed that TXA reduced intracranial haemorrhage growth compared to placebo. The effect of TXA on risk of death and other patient outcomes is uncertain.[46-48]

The CRASH-3 trial involving 12,737 patients with traumatic brain injury showed that early intravenous TXA treatment reduces head injury deaths. Early treatment of patients with complicated mild (GCS 13–15 with CT scan evidence of bleeding) and moderate traumatic brain injury conferred the greatest benefit. There was no increased risk of vascular occlusive events with TXA.[49]

Pulmonary haemorrhage

A systematic review including two small randomised trials found that TXA reduced the amount and duration of blood loss in patients with haemoptysis.[50] Another recent trial also suggests that using inhaled TXA can be safe and effective to control bleeding in patients with non-massive hemoptysis.[51]

Menorrhagia

Randomised trials of oral TXA show that it reduces blood loss in women with menorrhagia.[52]

Ocular haemorrhage

Randomised trials of oral TXA show that it reduces secondary haemorrhage in patients with hyphema.[53]

2 RATIONALE

2.1 Hypothesis for the trial

We hypothesise that IM and oral solution of TXA will be well absorbed in pregnant women. Based on PK modelling of data available in the literature, we predict that a 1 g IM injection or 4 g oral solution

administration of TXA will provide therapeutic TXA levels ≥10 mg/L[9] in plasma within about 30 minutes. We predict that the bioavailability of TXA administered via the IV, IM or oral solution routes will not be different from the bioavailability in healthy volunteers.

2.2 Description of trial population

Recruitment will continue until 120 women who are undergoing caesarean section with at least one risk factor for PPH and who complete the trial are included. 30 women will receive 1 gram of TXA by IV injection, 30 women will receive 1 gram of TXA by IM injection, 30 will receive 4 grams of TXA orally, and 30 will receive no TXA about 1 hour prior to the caesarean section. Additionally, women will receive routine interventions for active management of 3rd stage of labour and if they develop PPH, all standard interventions should be given. There are no restrictions on treatment of co-morbidities.

2.3 Name and description of the investigational medicinal product(s)

- **Intravenous route:** women will receive 1 gram tranexamic acid (100 mg/mL solution).
- **Intramuscular route:** women will receive 1 gram tranexamic acid (100 mg/mL solution) split between two 5-mL IM injections.
- **Oral liquid route:** women will receive 4 grams tranexamic acid (1 g/10 mL solution).

2.4 Description and justification of the dosage, route of administration, administration schedule and treatment duration

In this study, women will be randomised to four groups:

1. **IV TXA GROUP:** 30 women will receive 1 g of TXA by IV route. This route has been well characterised over the years, but the TXA PK and PD in pregnant women has not been described so far. IV TXA treatment rapidly achieves the plasma levels of TXA needed to inhibit fibrinolysis and prevent excessive bleeding. Pharmacological research has shown that an IV dose of 1 g TXA maintains therapeutic plasma levels for around 3 hours, the period when the risk of bleeding is greatest.[11,28]
2. **IM TXA GROUP:** 30 women will receive 1 g of TXA by IM route. Studies of IM TXA in healthy volunteers report good absorption and no adverse effects. The dose will be given as two 5 mL (0.5 g each) injections into the thigh (rectus femoris or vastus lateralis) or buttocks (gluteal muscles) muscles, depending on a clinical assessment of muscle mass.[11] The 1 g dose (10 mL) is divided to reduce the volume injected (5 mL is considered the upper limit).[54] See Section 4.1 for further information about administration of intramuscular TXA.

3. **TXA SOLUTION ORALLY:** 30 women will receive 4 g of TXA oral solution. The dose was selected because of the 50% oral bioavailability and because previous and preliminary PK data show that the absorption through the oral route is much slower than through the IV or IM routes, with also much lower maximal concentration (Cmax), therefore higher doses are needed to reach therapeutic levels, according to simulations. The oral route (tablets or solutions) is well characterised, but the oral TXA PK and PD in pregnant women has not been described so far.
4. **NO TXA CONTROL:** 30 women will receive no TXA and will be the control group for the pharmacodynamics, blood loss and safety data.

2.5 Safety of TXA and potential benefits and risks for study participants.

TXA is a widely used treatment with a good safety profile. Although on pathophysiological grounds we might expect an increased risk of thrombosis with antifibrinolytic drugs, randomised trials including over 50,000 participants show no increased risk.

TXA reduces the risk of death due to bleeding in women with PPH. The WOMAN trial randomised 20,060 women with PPH to receive TXA or placebo.[7] The results show that TXA reduces death due to bleeding (RR=0.81, 95% CI 0.65 to 1.00), particularly when given within three hours of giving birth (RR=0.69, 95% CI 0.52 to 0.91). There is also evidence from randomised trials that TXA improves outcomes in traumatic and surgical bleeding. The CRASH-2 trial of TXA in 20,211 bleeding trauma patients show that TXA reduces death due to bleeding when given soon after injury.[42,55] Combined data from the CRASH-2 and WOMAN trial (40,138 patients) indicate that TXA significantly increased overall survival from bleeding (odds ratio [OR]=1·20, 95% CI 1·08–1·33; p=0·001). Immediate treatment after injury/childbirth improved survival by more than 70% (OR=1·72, 95% CI 1·42–2·10; p<0·0001). Thereafter, the survival benefit decreases by 10% for every 15 min of treatment delay until 3 h, after which there was no benefit.[8] In surgery, a systematic review of 129 randomised trials found that TXA reduces the probability of receiving a blood transfusion by 38% (RR=0.62, 95% CI 0.58 to 0.68) and average blood loss by 34% (RR=0.66, 95% CI 0.65 to 0.67).[24,43]

TXA is widely used and well tolerated. Potential side-effects reported by manufacturers to be associated with use of TXA according to frequency are:[56,57]

- Common (≥1/100 to <1/10): diarrhoea, vomiting and nausea
- Uncommon (≥1/1000 to <1/100): dermatitis allergic
- Rare: hypersensitivity reactions including anaphylaxis; convulsions; visual disturbances including impaired colour vision; malaise with hypotension (generally following a too fast intravenous injection); arterial or venous thrombosis.

High doses of TXA (intravenous doses from 7.5 g up to 20 g) have been associated with seizures in cardiac surgery, but there was no increase in seizures in the CRASH-3 (12,737 patients) or WOMAN (20,060 patients) trials, which used doses of 1 or 2 grams intravenously.

TXA is excreted in the urine unchanged with 90% of the dose excreted in the 12 hours after administration. Plasma concentrations are higher in renal insufficiency and with repeated dosing there is a risk of accumulation. However, because a single dose of 1 g (intravenously or intramuscularly) or 4 g (orally) is used in the WOMAN-PharmacoTXA trial, there will be no risk of accumulation. Additionally, we will not include women with known renal impairment. There was no increased risk in adverse events with TXA in either the WOMAN trial and the CRASH-2 trial.

Women in the postpartum period are considered to be at increased risk of thromboembolic events compared with non-pregnant women. Although the absolute risk of venous thrombosis is low at around 2 per 1,000 woman-years, women in the postpartum period are four times more likely to suffer a venous thrombosis than non-pregnant women of the same age.[58] Randomised trials provide no evidence of any increased risk of venous thrombosis with TXA. In the WOMAN trial, the risk of venous thrombosis did not differ significantly between groups. Because severe bleeding is a strong risk factor for vascular occlusive events and TXA reduces bleeding, it is possible that TXA reduces (rather than increases) the risk of thrombosis.[59]

TXA passes into breast milk in very low concentrations, approximately one hundredth of the concentration in maternal blood.[40,60,61] One study reported that growth and development parameters were similar in children exposed to TXA through breastmilk compared to unexposed children, with no long-term adverse events.[60] No adverse events in breastfed babies were found in the WOMAN trial.[7]

TXA administered to pregnant women crosses the placenta and TXA concentration in the umbilical cord blood is similar to the concentration in the maternal blood.[62,63] The half-life of TXA in serum is 1-2 hours,[64] which would result in the elimination of TXA from the body within a few hours. Information is limited on the potential adverse effects on neonates of TXA administered to women before CS.

One study reported that no side effects were observed in new born babies from 12 healthy mothers who received TXA 10-20 min before CS delivery.[62] In three trials, 1 g of TXA was administered 10-20 minutes before CS, and no adverse events to mothers and neonates were reported in two of them.[40] One of the three studies reported that some mild and transient side effects occurred, but did not specify what kind of effects, how many participants were affected, and if any of these effects affected the babies.[65] A systematic review on the prophylactic use of TXA in cases of elective CS or abdominal myomectomy included 16 trials with a total of 2,949 patients (2,789 underwent CS).[38] Only one of the eligible studies reported thromboembolic events that occurred in two patients in the TXA group, and

two in the control group. This review did not report any side effects of prophylactic TXA on neonates. Similarly, a systematic review on the prophylactic use of TXA in women undergoing CS included 21 trials with a total of 3,852 patients.[66] Also this review did not report any adverse events in the mothers, except for the four cases of thromboembolic events reported in the same trial included in the previous review. A review on guidelines and relevant data on the use of TXA in PPH prophylaxis for CS and vaginal delivery reported that the only evidence of possible adverse events for the mother concerned poor renal outcome in a case series study with 18 patients with renal cortical necrosis in PPH where a TXA maintenance dose was used. The case series study reported that patients that did not recover normal renal function had a TXA maintenance dose of 0.5-1 g/h for a longer time (7.1 ± 4.8 h) compared to patients who recovered partial renal function (2.9 ± 2.4 h).[67,68] This review confirmed that there are no reports of adverse neonatal outcomes associated with the administration of TXA shortly before giving birth to prevent PPH.[67] A systematic review on the effectiveness and safety of the use of TXA to prevent PPH that included 25 studies with a total of 4,747 participants concluded that there was no increased risk of deep vein thrombosis and an increased risk of minor transient events, i.e. nausea, vomiting, headache or dizziness.[69] The included studies that evaluated the safety of TXA on neonates reported that no adverse events occurred, and the Apgar score that assesses the baby's health immediately after birth showed no difference between babies in TXA-treated and control groups.[69]

No mutagenic activity of TXA has been detected *in vitro* and *in vivo* test systems.[70] No foetal abnormalities were identified in early dysmorphology and reproductive studies in animals.[70-72]

As the TXA will be delivered at the end of the 3rd trimester of pregnancy when the foetal development is complete, the trial treatment will not have any impact on foetal development.

The foreseeable risks related to the IM route of administration may include pain, redness and bruising at the injection site and a rare risk of infection at the injection site.

The study also involves additional blood samples from all participants. We will take the smallest possible volume of blood which will allow us to carry out the analysis. The total volume of blood taken from the participating women (maximum of 35 mL over 24 hours) should have no clinical impact on the participant. One blood sample (2 x 10 μl) will be taken from the neonate at the time of the routine heel prick test.

We will routinely assess all women for nausea, vomiting, diarrhoea, thrombotic events, seizures and injection site reactions in all women as secondary outcomes. Additionally, all neonates will be routinely assessed for birth complications and adverse events.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objectives

- To assess the population pharmacokinetics of intravenous, intramuscular and oral TXA solution in pregnant women.

3.2 Secondary objectives

- To assess the effect of the three routes of TXA administration on D-dimer concentration in blood samples.
- To assess the concentration of TXA that crosses the placenta into the neonate via the three routes of administration.
- To assess clearance of any TXA in neonate
- To assess the safety of the three routes of TXA administration
- To assess the effect of the three routes of TXA administration on postpartum bleeding

3.3 Primary endpoints

- Blood TXA concentrations over time in pregnant women

3.4 Secondary endpoints

- Blood concentrations of D-dimer over time
- TXA concentration in umbilical cord and neonate after birth
- Local reactions at IM injection sites
- Adverse events (maternal and neonate)
- Neonate status Apgar score
- Measured blood loss from start of CS to 2 hours after
- Clinical diagnosis of PPH

4 TRIAL DESIGN

A prospective, randomised, open label study to be conducted in obstetric units in Pakistan and Zambia. Potential eligible participants will undergo C-sections. Consent will be obtained as per section 7.2 below.

4.1 Trial intervention

Participants will be randomised about 1 hour before CS to one of the following four groups:

1. 1 gram dose of TXA by IV injection about 1 hour before CS. Number of participants = 30
2. 1 gram dose of TXA by IM injection about 1 hour before CS. The IM dose will be given as two 5mL (0.5 g each) injections into the thigh (rectus femoris or vastus lateralis) or gluteal muscles,

depending on a clinical assessment of muscle mass. The 1 gram dose (10 mL) is divided to reduce the volume injected into each muscle (5 mL is considered the upper limit).[54] The injections will be given using the most appropriate needle size for IM administration from the sites stock (1" between 19 - 25 gauge and from 1 ½ inches up to 3" for large adults) using the Z-track method to seal the medication in the muscle.[54] Number of participants =30

3. 4 g of TXA solution orally about 1 h before CS. Number of participants = 30
4. No administration of TXA. Number of participants = 30

5 TRIAL SETTING

Participants will be recruited from obstetric units in Pakistan and Zambia. Recruitment, treatment and follow-up will be conducted at the recruiting obstetric units.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Women admitted to hospital giving birth by CS
- History of at least one risk factor for PPH
- Adult (≥18 years old)

6.2 Exclusion criteria

- Women giving birth vaginally
- Women with a known allergy to TXA or its excipients
- Women with current antepartum haemorrhage
- Women known to have received TXA within 48 hours prior to randomisation
- Women with known renal impairment
- Women with any known blood clotting disorder

7 TRIAL PROCEDURES

7.1 Screening of potential participants

Potential eligibility will be assessed by a clinician at the participating obstetric clinic when the woman is admitted for a CS.

7.2 Methods for informing and obtaining consent

7.2.1 Information giving

Women who are admitted for a CS with one risk factor for postpartum haemorrhage will be given oral and written information and fully informed consent will be obtained by the clinician. If she is unable to read or write, the information sheet will be read to her, and she will mark the consent form with a cross or thumbprint. In this case, an impartial witness must be present throughout the procedure and provide a signature confirming the mark.

The clinician will explain the trial to the woman verbally in a language that she understands and provide a written participant information sheet (Appendix 1). In brief, it will be explained that she will receive the usual care given to women having a caesarean section at the hospital. The clinician will explain that if she accepts to participate, because she is at risk of increased post-partum bleeding she will receive a drug called tranexamic acid into a vein, or a muscle, or to swallow it, or she may receive no trial drug. We need to study this because injecting TXA into a muscle or swallowing it are easier than injecting it into a vein.

This would mean that the treatment could help many more women giving birth who are at a high risk of bleeding. The clinician will explain to the woman the expected risks of the treatment to herself and the baby. If the woman objects to inclusion, her views will be respected. The clinician will explain to the woman that she has the right to withdraw from the trial at any time, without the need to justify the reason and without any consequences on the care provided to her and her baby. An overview of the consent procedure is provided in Appendix 2.

7.2.2 Documenting consent process

In all cases, the clinician obtaining consent should record in the participant's medical notes the method used for obtaining a participant's consent. The clinician should retain the original signed and dated consent form, a copy should be given to the woman.

7.3 Baseline data

The following baseline data will be recorded:

- Demographic (age) and anthropometric data (height and weight [body mass index and body surface area using the Du Bois formula will be derived]). Information on these parameters can be collected at baseline
- Medical and pregnancy history
- PPH risk factor(s)

- CS planned date and time
- Reason for CS
- Vital signs including blood pressure, temperature, heart rate, and respiratory rate
- Full blood count
- Blood test to assess renal function (urea, creatinine, estimated glomerular filtration rate)
- Any foetal abnormalities
- Any foetal distress

Baseline parameters will be used to build a pharmacokinetic model that describes the TXA concentration in the blood over time following TXA administration.

7.4 Randomisation

After collecting baseline data, enrolled participants will be randomised into one of the four groups described in section 4.1. The allocation sequence for each dosing cohort will be created using computer-generated random numbers, using blocking to ensure the required balance in the allocation of participants to treatment arms. The allocation ratio will be 1:1:1:1.

An IT coding expert supported by a statistician who are not involved in the conduct of the trial will prepare the randomisation codes. Eligibility will be confirmed and randomisation done via an online database. Once the code is generated, the trial intervention will be prepared and administered by a trained trial team member. Participants and all trial staff will be blind to treatment allocation until randomisation is completed.

7.5 TXA administration and timing of biological samples

The time of the TXA administration is T_0. One blood sample will be taken for pharmacokinetics prior to drug administration.

Post TXA administration blood samples will be taken as per the schedules below. We understand that the care of the participant takes priority over the sampling schema and that sample times will inevitably differ from those indicated. If it is not possible to obtain a sample at the scheduled time, the sample should be collected as soon as feasible with the exact time of collection recorded. Reasons for any delay will be recorded. Where there are less than 6 PK samples obtained after TXA administration from a participant, this participant will be replaced in the study.

Pharmacokinetics: Finger prick blood samples (2 x 10 μL per sample) for TXA quantitation will be taken as per the table below.

Pharmacodynamics: Blood samples (3 mL of venous blood in tubes containing 3.2% sodium citrate) for D-dimer quantitation will be taken as per the table below.

<table>
<tr><th colspan="4">Maternal blood samples</th><th>Placenta, cord and neonate(s) blood samples</th></tr>
<tr><td></td><td>FBC and Renal Function</td><td>PK</td><td>D-dimer</td><td rowspan="3">PK sample immediately after the umbilical cord is clamped</td></tr>
<tr><td>Baseline (after consent)</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>T_0 = TXA administration about 1 hour (± 30 min) prior to CS</td><td></td><td></td><td></td></tr>
<tr><td>$T_1 = T_0 + 15$ min (± 5 min)</td><td></td><td>x</td><td></td><td rowspan="8">PK sample from neonate when routine heel prick tests are obtained - as soon as possible after birth and no later than 24 hours</td></tr>
<tr><td>$T_2 = T_0 + 30$ min (± 15 min)</td><td></td><td>x</td><td></td></tr>
<tr><td>$T_3 = T_0 + 1$h (± 30 min)</td><td></td><td>x</td><td></td></tr>
<tr><td>$T_4 = T_0 + 2$h (± 1h)</td><td></td><td>x</td><td></td></tr>
<tr><td>$T_5 = T_0 + 4$h (± 1h)</td><td></td><td>x</td><td>x</td></tr>
<tr><td>$T_6 = T_0 + 8$h (±1h)</td><td></td><td>x</td><td>x</td></tr>
<tr><td>$T_7 = T_0 + 12$h (±2h)</td><td></td><td>x</td><td>x</td></tr>
<tr><td>$T_8 = T_0 + 24$h (±2h)</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td colspan="5"><u>NOTE:</u> Only one PK sample will be collected at baseline for those randomised to NO TXA. D-dimer, routine FBC and renal function will be collected.</td></tr>
</table>

7.6 Collection and storage of biological samples.

Only one blood sample for PK analysis will be collected at baseline for women who are randomised to receiving no tranexamic acid. Samples for D-dimer, full blood count and renal function will be collected.

Maternal blood will be taken from a cannula to avoid multiple venepuncture as follows:

Two samples of 3mL each will be taken for full blood count (FBC) and two samples of 3mL each for renal function. Blood samples will be collected in purple top EDTA tubes for FBC and yellow top tubes with separation gel and clot activator for renal function.

Five blood sample for D-dimer of 3 mL for each sample of blood to be taken in collection blue top tubes containing 3.2% sodium citrate. Blood samples for D-dimer, FBC, and renal function will be collected from the hospitals and analysed by the local central laboratory. The laboratory will be asked to store the sample used for D-dimer analysis until the end of trial to allow for repeat tests if needed.

In the event of failure of any of the PK samples, this will be used as a back-up and will be destroyed at the end of the trial.

Each maternal PK sample require about 20 µl of blood taken using a Mitra® cartridge from a finger prick (2 x 10 µL samples taken on the 2 cartridges of the same device to have one primary and one confirmation sample if needed). Sites will be provided with written procedures on how to obtain the blood sample using the Mitra® cartridge. Cartridges will be labelled with the date and time the sample was taken and with the participant Study Identification number.

The total volume of blood taken (less than 35 mL) should have no clinical impact on the patient.

To obtain the umbilical PK blood sample, once the umbilical cord is clamped, it is wiped with antiseptic and a syringe and needle is inserted into the vein in the umbilical cord to withdraw a small amount of blood. PK samples from the umbilical cord and neonates will be taken using the Mitra® cartridge system as described above.

A blood sample from the neonate (2x10 µL) will be taken using the Mitra® cartridge at the time of the routine clinical heel prick test to avoid additional heel pricks.

PK samples will be placed into suitable sealed biological sample shipping bags and sent weekly to Dr Grassin-Delyle's laboratory at UFR Simone Veil - Santé, University Versailles Saint Quentin (2 avenue de la source de la Bièvre, 78180 Montigny le Bretonneux, France) for PK analysis. No participant identifiable data will be transferred to the laboratory. Once all analyses for this trial have been completed, all blood samples will be destroyed.

7.7 Follow-up assessments

The following parameters will be assessed and recorded during the follow-up time of 7 days or until discharge whichever is earlier:

Maternal:

- **Blood lost:** Blood lost from incision to 2 hours after the CS will be estimated. The amount of blood in sponges and drapes used in surgery and blood loss from suctioning (excluding amniotic fluid) will be estimated. At the end of surgery, a calibrated obstetric drape will be used for 2 hours.
- **Reaction at site of IM injections**: Each IM injection site will be inspected for local reactions at the same time as PK blood sampling and then daily thereafter (for 7 days or until prior discharge).
- **Vital signs**: Participants will have their blood pressure, temperature, heart rate and respiratory rate recorded at the time of each PK blood sampling and daily until discharge or day 7.

- **Treatments:** Data on treatments likely to influence PK levels of TXA (blood product transfusion and IV fluids administration, TXA or other antifibrinolytics) will be collected from the time of TXA administration up to the time of the last PK sample.
- **Adverse events:** As described in Section 9, will be recorded up to 7 days.
- **Clinical Diagnosis of PPH:** Clinical diagnosis of PPH up to 24 hours after birth (total blood loss of >1000 mL, or any blood loss sufficient to cause haemodynamic instability or requires further treatment).

Neonate:

- **Apgar score** recorded 1 and 5 minutes after birth. This is a standard clinical test given to all newborns. This test checks a baby's heart rate, muscle tone, and other signs to see if extra medical care or emergency care is needed.
- **Adverse events:** As described in Section 9, will be recorded up to 7 days.

7.8 End of trial for participants

The trial ends at discharge, death or at 7 days, whichever occurs first.

7.9 Summary of trial procedures

Procedure	**Baseline** Arrival at hospital up to 1 hour before CS	**Immediately before TXA administration** (1 hour before CS)	**1 hour (± 30 min) before CS** (TXA administration)	**Follow-up** After TXA administration to 24 hours after	**Follow-up** (Discharge, death or Day 7, whichever comes first)
Initial eligibility assessment from medical records	X				
Consent	X				
Baseline data and blood sample collection: • Demographics and anthropometric data • Vital signs (blood pressure, temperature, heart rate, respiratory rate) • Medical and obstetric history • Blood test: Full blood count, renal function, D-dimer, PK • Foetal status (alive or dead, abnormalities, congenital or genetic problems)	X				
Confirm eligibility	X				
Randomisation	X				
TXA administration as per randomisation			X		
Maternal Blood samples: • Blood samples post-TXA for PK at different time points over a period of 24 h. • Blood sample for D-dimer				X	
Post randomisation blood sample for FBC and renal function				X	
Reaction at IM injection sites assessment				X	X

Vital signs: • Blood pressure • Temperature • Respiratory rate • Heart rate	X			X	X
Concomitant treatments (interventions for prevention and treatment of PPH, blood products and IV fluids)				X	
Measure of blood loss within first 2 hours after CS				X	
Clinical diagnosis of PPH			X	X	X
Interventions for prevention and treatment of PPH				X	X
Maternal adverse events				X	X
Neonate status at birth				X	
Cord blood sample when umbilical cord is clamped				X	
Neonate Apgar score				X	
Adverse events in neonate				X	X
Blood Sample from neonate (routine heel prick test)				X	

7.10 Distinction between standard care and research

The only departure from standard care is the TXA given about 1 hour prior to CS and extra blood sampling. Additionally, we will regularly inspect the IM injection sites.

7.11 Blood samples analysis

7.11.1 TXA quantitation

TXA will be measured with liquid chromatography coupled to mass spectrometry according to an analytical method validated following the EMA guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009Rev.1 Corr.2)[73]. The method is linear in the range 1.0-1000.0 µg/mL, accuracy is between 88.4 and 96.6% and precision <3.0%.

7.11.2 D-dimer quantitation

Blood for D-dimer assays will be assayed at a central laboratory. A citrate-containing tube will be properly filled and mixed via inversion. It will be transported to the laboratory and analysed within 3 hours. Quantification will be done by immunoassay.

7.12 Premature exit of trial participant

Participants may exit the study at any time and for any reason. A previously given consent can be withdrawn. The investigator can withdraw a participant from the trial for any safety reason or if it is in the participant's best interest.

If a participant exits the trial prematurely or withdraws consent or refuses consent for continuation, data collected up to time of premature exit will be used. Participants who withdraw from the trial with less than 6 post treatment PK samples will be replaced to ensure the four intervention groups remain balanced.

7.12.1 Monitoring participants after the premature termination of treatment

In case of an adverse event to the participant or her baby, the investigator will complete an adverse event report and monitor the event until the end of her participation in the research or until it has resolved or reached a stable state.

7.12.2 Procedure for replacing participants

If consent procedures are complete but the TXA dose is not given in full, the participant will be replaced.

When oral TXA is given and the participant vomits within the first hour of receiving the intervention, this participant will be replaced in the study. However, data collection for the participant will continue to the trial end.

Where the CS is delayed and takes place more than 2 hours after the administration of the intervention, the participant will be replaced in the study. However, data collection for the participant will continue to the trial end.

If a participant receives the TXA dose but there are less than 6 post treatment evaluable PK samples obtained after TXA administration, this participant will be replaced in the study. However, data collection for the participant will continue to the trial end.

Data collected from the replaced patients will be used.

7.12.3 Full or partial discontinuation of the study

LSHTM (the Sponsor) may prematurely discontinue all or part of the trial, temporarily or permanently, in the following situations:

- If new information about the trial drug, in light of which the objectives of the study are unlikely to be achieved.
- LSHTM reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

If the trial is discontinued prematurely, the LSHTM Clinical Trials Unit (CTU) will inform the relevant Regulatory Authorities and Ethics Committees of its decision within 15 days, together with justification for the decision.

8 TRIAL DRUGS

8.1 Description and regulatory status of investigational medicinal product(s)

TXA is sold globally under a variety of trade names for the treatment of bleeding due to general or local fibrinolysis in adults and children from one year of age.[57] Several brands are licenced for use globally. TXA which has Marketing Authorisation from the Regulatory Authority will be purchased locally in the participating country .

Participants will receive a marketed form of tranexamic acid.

8.2 Preparation, labelling and instruction for administration of trial intervention

Participants will receive the tranexamic acid at a concentration of 0.5 g/5mL solution.

Labelling: The outer package of the tranexamic acid will be over-labelled by a qualified Pharmacist with the following label: 'WOMAN-PharmacoTXA trial for clinical trial use only'. The original manufacturer labelling will not be altered in any other way. When a participant is randomised, written instructions will appear on the computer screen and it will also be sent by email to the person randomising the participant, the Principal Investigator and the LSHTM CTU. Instructions will be as follows:

If randomised to Intravenous administration of TXA: *This participant has been randomised to INTRAVENOUS ADMINISTRATION OF TRANEXAMIC ACID. Please take TWO ampoules of 0.5 g/5mL. Draw up both ampoules in a 10 mL syringe and administer as an intravenous injection at a rate of 1mL per minute. Please ensure relevant blood sample is taken beforehand.*

If randomised to intramuscular administration of TXA: *This participant has been randomised to INTRAMUSCULAR ADMINISTRATION OF TRANEXAMIC ACID. Please take TWO ampoules of 0.5 g/5mL. Draw up EACH ampoule separately in two 5 mL syringes. Please administer as two separate injections into the injections into the thigh (rectus femoris or vastus lateralis) or buttocks (gluteal muscles) muscles, depending on a clinical assessment of muscle mass. Please ensure relevant blood sample is taken beforehand.*

If randomised to oral solution of TXA: *This participant has been randomised to ORAL SOLUTION ADMINISTRATION OF TRANEXAMIC ACID. Please take EIGHT ampoules of 0.5 g/5mL tranexamic acid. Using a syringe, draw up the contents of all eight ampoules (total volume 40 mL) and place in a medicine cup. Please ask the woman to drink the whole amount. Participants will be offered a mouth rinse to remove the taste of TXA. Please ensure relevant blood sample is taken beforehand.*

If randomised to no TXA: *This participant has been randomised to receive NO tranexamic acid. Please continue to provide standard care.*

Accountability: Together with a qualified pharmacist (QP), the National Coordinator/National Principal Investigator will be responsible for purchasing 500 x 5mL ampoules of 0.5 g/5mL tranexamic acid from an approved source in each country. The QP will be responsible for adding a label to the IMP box: '*WOMAN-PharmacoTXA trial for clinical trial use only*'. The original manufacturer labelling will not be altered in any other way. The drug will be double checked with the qualified pharmacist by LSHTM-CTU. The manufacturer, quantity, batch number, expiry date and additional label will be checked and recorded. The drug will be stored in accordance with the temperature recommendation of the manufacturer until dispatch.

LSHTM-CTU will instruct the QP when to send the IMP and the quantity needed to trial sites. Records of all requests for shipment and all shipments made will be maintained by the QP and stored with the National Coordinating Investigator of each country and copies sent to LSHTM-CTU. If the IMP stock received is unexpected, wrong or damaged, the stock should be quarantined by the site and LSHTM CTU contacted for further actions.

Storage conditions and supply: In advance of the trial start, the site pharmacist/delegate will carry out a risk assessment of suitable storage in the obstetric units to ensure the trial drug is available for use without delay. Although TXA is heat stable, it will be stored in a dry place where it is protected from excessive heat and freezing.

Sites will have to report all used trial drugs and those that are lost or damaged, to LSHTM-CTU on a Drug Accountability Log.

8.3 Known drug reactions and interaction with other therapies

TXA solution for injection should not be added to blood for transfusion, or to injections containing penicillin.

8.4 Trial restrictions and the use of concomitant medication

Participants should receive all clinically indicated treatments. There is no restriction on the use of concomitant medication. In the event non-trial TXA is given during the time of the PK blood sampling, the dose, route of administration, date and time should be recorded on the Case Report Form (CRF).

8.5 Assessment of compliance with treatment

IV, IM or oral TXA will be given by investigators at the participating site who will record the date and time of administration and who administered the IMP. For the IM route, the body location of each TXA injection will also be recorded. If only one or none of the ampoules is administered, the reason for this will be recorded in the CRF. The following will not be considered non-compliance with the protocol: where a participant dies before receipt of the IMP or where a clinical or protocol allowed reason is given for non-administration of the IMP.

9 PHARMACOVIGILANCE

Maternal events which occur as a consequence of the CS, or events which commonly occur in this population independent of exposure to the TXA administration, and those which are study endpoints do not need to be reported as an adverse event. Congenital or genetic abnormalities in neonates do not need to be reported as adverse events as these events are collected routinely. All other events fulfilling the criteria below should be reported. If a participant (both maternal and neonate) develops an adverse event, they should be treated in line with local procedures. In the definition below, participant refers to both maternal and neonate (s).

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease having been absent at baseline, or if present at baseline, appears to worsen AND is temporally associated with medical treatment or procedure.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in Investigator Brochure (IB). It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.

Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • The Reference Safety Information to be used for this trial is the IB.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 The role of the site investigator

The investigator must assess the seriousness criteria of each adverse event and record all serious and non-serious adverse events in the CRF.

The investigator must document serious adverse events as thoroughly as possible and provide a definitive medical diagnosis, if possible. Additionally, the causal relationship between the serious adverse events and the IMP is needed.

When completing the Adverse Event reporting form, the investigator will assign a causality using the definitions in the table below.

Relationship	Description
Suspected to be related	There is evidence to suggest a causal relationship with administration of the trial treatment and the influence of other factors is unlikely.
Not suspected to be related	There is little or no evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

If there is any doubt about the causality, the site Principal Investigator (PI) or medical delegate will inform the LSHTM CTU. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, both points of view are to be recorded and reported onwards as required.

9.2.1 Serious adverse events

The investigator must notify the LSHTM CTU **within 24 hours of the investigator becoming aware** of any adverse event which is assessed as being serious (see SAE definition in section 9.1).

9.2.2 Period during which the investigator must notify the Sponsor of SAEs

The investigator will notify LSHTM CTU without delay of all serious adverse events:

- starting from administration of the trial drug
- throughout the whole follow-up period

9.2.3 Procedures and deadlines for notifying the Sponsor of SAEs

The investigator should complete a SAE report form. This report must be signed by the investigator.

The investigator should provide as much information as possible on the SAE form so that the Sponsor can carry out assessment for onward reporting.

The initial report must be followed up by one or more additional written reports describing the course of the event and any additional information required by the sponsor.

Whenever possible, the investigator will provide LSHTM CTU with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized and the study acronym, the trial participant screening ID number written on each document provided.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has terminated his/her participation in the trial.

The initial SAE report, follow-up reports, and all other documents must be entered directly onto the trial database (eCRF) or sent to the LSHTM CTU by e-mail (WomanPTXA@Lshtm.ac.uk).

When using the eCRF:

- The investigator completes the SAE report form in the eCRF, then validates, prints and signs the form for the ISF.
- In case of failure to connect to the eCRF, the investigator should complete, sign and send a paper CRF by email to WomanPTXA@Lshtm.ac.uk. In this case, LSHTM CTU will enter the SAE report form in the eCRF.

The investigator must comply with all requests for additional information from relevant authorities.

For urgent questions relating to an adverse event report, please contact LSHTM CTU using the emergency phone number in the ISF.

9.3 Role of the Sponsor

The Sponsor, represented by LSHTM CTU, shall continuously assess the safety of the IMP throughout the trial.

9.3.1 Assessment and declaration of serious adverse events

The LSHTM CTU is responsible for assessing:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and IMP and/or study procedures and any other treatments,
    - all serious adverse events for which the investigator and/or the Sponsor suspect a causal relationship with the IMP are classed as suspected serious adverse reactions.
- the **expectedness assessment** of the serious adverse reactions
    - any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the IB, is considered unexpected.
    - the expectedness of the serious adverse reaction based on the IB.

Any suspected unexpected serious adverse reaction (SUSAR) will be subject to expedited reporting to each participating Regulatory Authority, Ethics Committees and the Sponsor within seven working days of being reported to the CTU.

LSHTM CTU will notify all the site PIs about any information reported that could adversely affect the safety of the trial participants.

9.3.2 Analysis and declaration of other safety data

In the event new safety data becomes available, a reassessment of the risk/benefit ratio of the trial or the IMP will be done by the Sponsor.

The Sponsor will inform relevant Regulatory Authority and Ethics Committees without delay if it becomes aware of any safety issue and, if applicable, describe which measures have been taken.

9.3.3 Annual safety report

The Sponsor will prepare once yearly throughout the trial duration an annual safety report which will be submitted on the anniversary of the regulatory approval which will include, in particular:

- an analysis of safety data concerning trial participants
- a description of the participants included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial

9.4 Data Monitoring Committee (DMC)

The DMC will review on a regular basis accumulating safety data (adverse events and injection site reactions) from the ongoing trial, and advise Chief Investigators regarding the continuing safety of current participants and those yet to be recruited. The Sponsor will remain overall responsible for the ongoing safety of participants in the trial. The roles and responsibilities of the DMC are detailed in Section 15.

9.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the participating Regulatory Authorities and Ethics Committees of the measures taken and the circumstances giving rise to those measures.

9.6 The type and duration of the follow-up of participants after adverse reactions.

Each IM injection site will be monitored as detailed in section 7.7.

Adverse events in the participant and her baby(ies) will be monitored up to day 7 or until death or discharge whichever is earlier.

Any SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred. All adverse events will need to be followed up until it has resolved or has reached a stable state.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

Using PFIM 3.2.1 software [74] and based on the population pharmacokinetic parameters determined in a meta-analysis of the different pharmacokinetic studies published in healthy volunteers and data through the IV route in trauma patients [30,75], a sample size of 120 participants will allow estimates (Relative Standard Errors < 30%) of the pharmacokinetic parameters of the intravenous, intramuscular and oral administration of TXA. Optimal maternal blood sampling times were evaluated and are as follows: immediately before TXA administration, and 15, 30 minutes, 1h, 2h, 4h, 8h, 12h and 24h after TXA administration. However, if in exceptional circumstances a sample cannot be taken at the optimal stated time, flexibility in blood sampling is allowed as detailed in the section 7.5. The actual sampling time must be recorded.

10.2 Planned recruitment rate

Pregnant women will be enrolled until 120 participants with fully evaluable data are included. Evaluable participants must receive the full dose, not vomit the oral dose within 1 hour of administration, and have at least 6 post randomisation PK blood samples.

10.3 Statistical analysis plan

All statistical calculations will be performed using STATA, unless otherwise specified. All data will be presented in the form of summaries sorted by treatment group (cohort) and patient ID. Tabular summaries will be presented based on the following grouping: IM, IV, Oral solution and No TXA.

For continuous variables, summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum values. Frequencies and percentages will be calculated for categorical variables.

10.3.1 Pharmacokinetic analysis

All participants who receive the full dose of TXA and did not vomit the oral dose within the first hour and have at least six PK samples obtained after TXA administration to determine maternal plasma concentrations of TXA will be included in the PK data analysis. The actual blood sampling times will be recorded and used in calculations for PK parameter estimation.

TXA time-courses will be analysed using the nonlinear mixed effect modelling software program Monolix 2019R2 version (www.lixoft.eu)[76], as previously described.[75,77-79] Briefly, parameters will be estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined to a Markov Chain Monte Carlo (MCMC) procedure (to ensure full convergence, the MCMC will be fixed to 20 and the iteration number to 1000). Different error models will be investigated (i.e. multiplicative, proportional and/or additive error models) to describe residual variabilities (expressed as σ, square root of σ^2), and the between-subject variabilities (expressed as ω, square root of the variance ω^2) will be ascribed to an exponential model. The Bayesian information criterion (BIC) will be used to test different hypotheses regarding the model, i.e.:

i. covariate effect(s) on pharmacokinetic parameter(s)
ii. residual variability model (proportional versus proportional plus additive model)
iii. structure of the variance-covariance matrix for the ω parameters.

Main covariates of interest in the population will be age, bodyweight (BW) and renal function, IV fluid and blood transfusion volume. Parameter estimates will be standardised for a mean standard covariate using an allometric model: $P_i = P_{STD} \times (COV_i/COV_{STD})^{PWR}$ where P_{STD} is the standard value of parameter and P_i and COV_i are the parameter and covariate values of the i^{th} individual. The PWR exponents may be estimated from the data. However, for bodyweight, allometric scaling theory dictates that these are typically 0.75 and 1 for clearance and volumes terms respectively.[46] The goodness-of-fit of each model will be evaluated by visual inspection of the individual concentration-time courses, the observed-predicted (population and individual) concentration scatter plots and the prediction-corrected visual predictive checks.

Placenta transfer and neonate heel prick PK levels: Concentrations will be presented in tabular form with mean, median, standard deviation and range as appropriate. For each time point, comparisons across groups will be done using the analysis of variance. We will adjust for time between drug

administration and sampling. Where both an umbilical cord and neonate heel prick sample is available, these will be used to build a PK model with gestational age and birth weight as the main covariates.

10.3.2 Pharmacodynamic analysis

D-dimer: Descriptive statistics for D-dimer concentration in maternal blood will be presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate. For each time point, comparisons across groups will be done using the analysis of variance. The PK data will be combined, and analyses may be conducted to determine a relationship between exposure and the effect on D-dimers.

10.3.3 Safety Parameters

Full blood count and renal function parameters: Descriptive statistics for baseline and follow-up will be presented for each laboratory parameter. Changes from baseline as well as shift tables for laboratory parameters will be presented. All laboratory values will be classified as normal, below normal (low), or above normal (high) based on normal ranges supplied by the central laboratory. Frequencies of abnormal values will be presented in tabular form. For purposes of analyses, laboratory results based upon standardized units will be used.

Vital signs: Descriptive statistics for blood pressures, heart, and respiratory rate will be presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate. Number (%) of women with abnormal values in each randomised group will be presented.

Expected adverse events (collected routinely as outcomes for all participant): For each event, the number (%) of women in each randomised group will be presented.

Other adverse events: AEs will be coded by primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events (n) and number (%) of patients with events will be presented. Events will be presented separately for maternal and neonates.

IM injection skin reaction: Number (%) of women with a reaction and severity of reaction will be presented.

10.3.4 Efficacy:

Blood loss at 2 hours: Descriptive statistics for maternal blood loss at 2 hours post-partum and total blood loss will be presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate. Comparisons across groups will be done using the analysis of variance.

Clinical diagnosis of PPH: Number (%) of women in each randomised group will be presented.

10.3.5 Interim analysis

There are no planned interim analyses.

10.3.6 Procedure(s) to account for missing data

If one or more blood samples are not collected, the reason for this will be recorded in the CRF.

Individual missing covariate data will be ignored in the pharmacokinetics mode

11 DATA MANAGEMENT

11.1 Data collection

Information required in the research protocol will be collected first onto a paper CRF and transferred to an electronic case report form (eCRF). An explanation should be given by the investigator for each missing data. Correction of discordant data on the eCRF will be resolved through queries. In the eCRF, the changes in the data will be tracked. Anonymization of the patients will be ensured by using the trial participant's screening number as their unique ID. This will be recorded on each document needed for the research.

11.2 Source data

Source documents include, but are not limited to, hospital records (from which medical history, previous and concurrent medication, clinical outcomes and adverse events may be reported onto the CRFs), clinical and office log books, laboratory and pharmacy records, diaries and correspondence.
CRF entries will be considered source data if data are entered directly onto the CRF as original recording (e.g. PK samples). Trial data will be kept confidential and stored securely. On all trial-specific documents, other than the consent form, the participant will be referred to by the trial participant screening ID number and not by name.

11.2.1 Case report forms

Case Report Forms (CRF) to collect data and SAE report forms that will be used in this trial is not included in this protocol and is provided separately.

11.3 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by

the hospitals in the case of hospital medical records, for the statutory period. The Sponsor requires source documents to be kept for 10 years after the end of trial declaration.

11.4 Data Recording and Record Keeping

All trial data will be entered on to paper CRFs and then entered onto the trial database by authorised site staff. The participants will be identified by a unique trial specific number. The name and any other identifying detail will not be included in trial data electronic file used for analysis or publication. An ISF containing the essential documents for the trial will be provided by the CTU. The ISF must be updated by the trial site throughout the course of the trial.

11.5 Access to Source Data

Appropriate agreement will be in place in advance of trial start to allow all parties involved in the study direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the Sponsor's quality control and audit procedures.

Site investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force.

11.6 Data confidentiality

The persons responsible for the quality control of the trial will take all necessary precautions to ensure the confidentiality of information relating to the IMP, the study, the study participants and in particular the identity of the participants and the results obtained.

These persons, as well as the site investigators themselves, are bound by professional secrecy.

During and after the clinical study, all data collected about the study participants and sent to LSHTM CTU by the investigators (or sent to other collaborators) will be anonymised.

Under no circumstances will the names and addresses of patients be shown.

The trial will comply with relevant Data Protection regulations including the European Union General Data Protection Regulation.

The Sponsor will ensure that appropriate consent is in place to access any personal information about the patient which is necessary for the quality control of the study.

11.7 Data processing and storage of documents and data

11.7.1 Data entry

Data will be entered electronically directly on to the trial database held by LSHTM CTU.

11.7.2 Data processing outside of the UK

Blood samples will be processed within the European Union (France). Anonymised data will be sent within the European Union for analysis.

11.7.3 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the Sponsor for 10 years after the end of the trial. LSHTM CTU are not able to archive source data or the ISF for participating sites, however costs associated with archiving will be considered in the site agreement.

11.7.4 Ownership of the data

LSHTM is the owner of the data of this trial. The data cannot be used or disclosed to a third party without its prior permission.

12 MONITORING, AUDIT & INSPECTION

12.1 General organisation

The Sponsor (LSHTM) will ensure the safety and respect of individuals who have agreed to participate in the trial. The Sponsor have in place quality assurance systems for monitoring the implementation of the study at the study sites.

12.2 Strategy for site opening

Participating investigators and trial sites have been identified from the network of obstetricians that was established during the WOMAN and WOMAN-2 trials. Before the trial can start at any site, all relevant regulatory and ethics approvals must be in place and the site Principal Investigator must agree to conduct the trial according to the Protocol, Good Clinical Practice guidelines and all the relevant regulations. Recruitment to the trial can only start once IMP have been released and the sites have been trained on the protocol and trial procedures.

12.3 Monitoring

The trial will be conducted in accordance with the current approved protocol, ICH-GCP, each participating country's relevant regulations and the Trial's written procedures. A monitoring plan will be made based on the risks identified in the Risk Assessment. The LSHTM CTU or country delegate will monitor the trial to ensure the rights, safety, and wellbeing of the trial participants and to ensure the accuracy of the data. All site investigators will be trained in the trial procedures and have extensive guidance. LSHTM CTU will require investigators and their institutions to provide access to source data and documents and all trial related documents for monitoring, audits, ethics committees review and regulatory inspection. All trial-related and source documents including medical records, original consent forms and original CRFs must be kept safely. Investigators must plan in advance of the trial start where the trial-related documents will be stored and how they will be accessed. All documents must be made available when required for monitoring/audit/inspection during the course of the trial and for up to 10 years after the end of the overall trial.

12.4 Case report form

All information required by the protocol will be entered onto paper CRFs and then in the eCRFs. The trial sites will have access to the eCRFs via a web-based data collection system. Access will be by individual unique username and password. Automatic consistency checks will ensure the data are verified immediately upon entry. An audit trail will be kept of all changes.

12.5 Management of non-compliances

Any events that occur as a result of the investigators or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures, good clinical practice or statutory and regulatory requirements must be recorded on a 'Breach Form' and sent to LSHTM CTU. Additionally, any local institutional procedures in relation to non-compliance must be followed.

LSHTM CTU has its own procedures for managing these non-compliances. All non-compliances must be reported to the Sponsor as soon as possible, and no later than 24 hours of identifying a non-compliance has occurred.

A "serious breach" is a breach which is likely to affect to a significant degree:

a) The safety or physical or mental integrity of the participants of the trial; or
b) The scientific value of the trial

In the event that a serious breach is suspected, the site must inform the CTU within one working day of becoming aware of the event. The CTU will report all serious breaches to the relevant REC committees, regulatory authorities within the timeline required by the participating country.

12.6 Audits/inspections

The Sponsor will also be responsible for auditing all aspects of the trial. The site PIs agree to accept the quality assurance audits carried out by the Sponsor as well as the inspections carried out by the MHRA. All data, documents and reports may be subject to regulatory audits and inspections. An audit can be carried out at any time by independent individuals appointed by the Sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force. The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

12.7 Principal Investigator's responsibilities

Coordination within each participating hospital will be through a site PI whose responsibility will be detailed in an agreement in advance of starting the trial and will include:

- personally supervise the study at site;
- before and if needed during the trial, obtain all institutional appropriate approvals / favourable opinion
- delegate trial related responsibilities only to suitably trained and qualified personnel;
- document delegation of duties to appropriately qualified persons;
- train relevant medical, nursing and other staff to ensure that they remain aware of the state of the current knowledge, the trial and its procedures;
- agree to comply with the final trial Protocol and any relevant amendments;
- ensure that all potentially eligible patients are considered promptly for the trial;
- ensure consent is obtained in line with approved procedures;
- ensure that the data are collected, completed and transmitted to the CTU in a timely manner;
- ensure all adverse events are reported promptly to the CTU;
- ensure blood samples are collected and prepared in line with the protocol and trial guidance;
- ensure the Investigator Site File is up-to-date and complete;
- account for trial drug at their site;
- ensure appropriate storage of trial drug;
- ensure the trial is conducted in accordance with ICH GCP and relevant country-specific regulations including clinical trial regulations and data protection laws;
- allow access to source data, including participants' medical records for monitoring, audit and inspection;

- be responsible for archiving all original trial documents including medical records, investigator's study file, consent forms and data forms for at 10 years after the end of the trial.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Consent

Please, see section 7.2 for details on methods for informing and obtaining consent from the research participants.

13.2 Legal obligations

13.2.1 The Sponsor's role

This trial is sponsored by the LSHTM and its responsibilities coordinated by the LSHTM CTU. The CTU may delegate responsibilities to third parties which will be outlined in relevant agreements. The responsibilities of the CTU will be overseen by the Trial Management Group with day to day responsibilities with the Trial Manager.

13.2.2 Request for approval

Approval from all relevant National and Local Ethics Committee will be obtained including LSHTM, sites and county level. Additionally, approval from the relevant drug regulatory agencies will be obtained as required.

13.2.3 Modifications to the trial

Any substantial amendment which may be needed to the protocol must be approved by the Sponsor. After approval is given, prior to implementing the amendment, approval from the relevant Regulatory Authorities and Ethics Committees must be obtained.

The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

13.2.4 End of study and final study report

The end of the trial is defined as the date on which data for all participants is locked and data entry privileges are withdrawn from the trial database. A declaration of the end of a clinical trial will be sent to the relevant Regulatory Authorities within 90 days of the end of the trial.

A final study report will be to be sent to relevant Regulatory Authorities and Ethics Committees within one year of the end of the trial.

13.3 Peer review

The trial was funded after an open competition with blinded peer review by Wellcome and Bill & Melinda Gates Foundation.

13.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation is obtained from relevant Regulatory Authorities and Ethics Committees and a favourable opinion is received.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the study, the CIs/PI or designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the CI or designee, in agreement with the Sponsor will submit an application to the appropriate bodies for review and approval. The CI or designee will work with sites so they can put the necessary arrangements in place to implement the amendment.

13.5 Protocol compliance

Please, see section 12.5.

13.6 Data protection and patient confidentiality

Please, see section 11.6.

13.7 Financial and other competing interests for the Chief Investigator, PIs at each site and committee members for the overall trial management

The personnel involved in this trial has no financial or other competing interests to disclose.

13.8 Indemnity

13.8.1 Sources of funding for the trial

LSHTM has received funding from Wellcome and Bill & Melinda Gates Foundation. The study is being conducted as an academic collaboration between LSHTM, participating obstetric units in Pakistan and Zambia and UFR Simone Veil - Santé, University Versailles Saint Quentin, France.

13.8.2 Insurance

LSHTM accepts responsibility attached to its sponsorship of the trial and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this trial. The indemnity is renewed on an annual basis and LSHTM assures that it will continue renewal of the indemnity for the duration of this trial.

13.9 Access to the final trial dataset

Each site will have continuous access to their own data as the trial is ongoing. The final dataset will be reviewed and published by group authorship consisting of members of the Protocol Committee and key participating site collaborators.

Once all pre-planned analyses are completed, the totally anonymised dataset, protocol, published manuscript, data dictionary and any other relevant trial documents will be made freely available on the LSHTM CTU data platform: https://ctu-app.lshtm.ac.uk/freebird/

14 DISSEMINATION POLICY

14.1 Dissemination policy

As Sponsor, LSHTM has the right and responsibility to ensure the results of this study are published. The main publication will be done as a group authorship consisting of the Protocol Committee. Once the pre-specified analysis is completed and data made freely available, anyone can use the trial data.

A final study report will be to be sent to the relevant Regulatory Authorities and Ethics Committees within one year of the end of the trial.

There are no plans to notify all participants of the outcome of the trial. However, participants can request a copy of the final results and each site will maintain a log of patients/families who would like a copy. LSHTM CTU provide copies to each site to send onwards.

14.1.1 Funders' acknowledgements

LSHTM has a legal responsibility to acknowledge in all relevant publications that they received funding from the Wellcome and Bill & Melinda Gates Foundation.

Funders do not have review and publication rights of the data from the trial.

14.2 Authorship eligibility guidelines and any intended use of professional writers

This study is being conducted as an academic collaboration. All parties who contribute significantly to this study will be named in the final publication.

Professional medical writers will not be hired to write dissemination material about the results of this trial.

15 ROLES AND RESPONSIBILITIES

i. FUNDING AND SUPPORT IN KIND

This trial is funded by Wellcome and the Bill & Melinda Gates Foundation.

ii. ROLE OF TRIAL SPONSOR AND FUNDER

The funders had no role in the design of the trial and will not have a role in its conduct, data collection, analysis, and interpretation, manuscript preparation, review, and approval, and publication of the results. The Sponsor is responsible for the approval of any substantial amendment which may be needed to the protocol. After approval is given, the Sponsor must obtain, prior to implementing the amendment, approval from the relevant Regulatory Authorities and Ethics Committees. The Sponsor is responsible for reporting serious adverse events as per each country's requirement and all serious breaches to relevant Regulatory Authority and Ethics Committees.

iii. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT GROUPS & INDIVIDUALS

Protocol Development Committee: This includes the Chief Investigators (CIs), site Principal Investigators (PIs) and participating clinicians and study staff. Its role is to ensure that the study protocol is scientifically appropriate and that all ethical, regulatory and scientific aspects of the trial have been considered. If the protocol requires amending, this committee will review and recommend any changes. The final decision for any amendment to the protocol resides with the Sponsor.

Members of the Protocol Development Committee:

- Haleema Shakur-Still: Study design, drafting and finalising the protocol
- Ian Roberts: Study design, drafting the protocol and finalising the protocol
- Rizwana Chaudhri: Study design
- Stanislas Grassin-Delyle: Pharmacokinetic methods and analysis
- Roberto Picetti: Study design and drafting the protocol
- Monica Arribas: Study design and drafting the protocol

Data Monitoring Committee (DMC):

The primary responsibility for monitoring and final decisions about safety of participants in the trial lies with the Sponsor. Independent oversight of the safety of participants will be provided by an independent DMC. The composition of the DMC is provided in Appendix 3.

The DMC will review on a regular basis accumulating safety data (adverse events and injection site reactions) from the ongoing trial, and advise Chief Investigators regarding the continuing safety of current participants and those yet to be recruited. Data on the type, frequency and severity of AEs in mother and neonate will be reported to the DMC.

The DMC membership includes expertise in clinical trials, the use of tranexamic in obstetrics and gynaecology, care of women during childbirth and postnatal period and care of the newborn. The committee members are familiar with the safety profile of the drug.

The DMC Charter includes, but is not limited to, defining:

- the schedule and format of the DMC meetings;
- the format for presentation of data;
- the method and timing of providing interim reports.

The DMC members are independent of the Sponsor, ethics committees, regulatory agencies, investigators, clinical care of the trial participants, and all trial operations.

Trial Management Group: The Trial Management Group will comprise the CI, trial manager, data manager and statistical expert. They will have responsibility for the day to day management of the trial. They will meet regularly to ensure that the trial is progressing according to the protocol.

16 REFERENCES

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17 PROTOCOL VERSION CHANGES

Summary of changes between version 1.1 and 1.2

Protocol Section	Description of change
KEY TRIAL CONTACTS	Addition of Zambia as a participating country. **Addition of:** Details of the National Principal Investigator in Zambia **Addition of :** Details of the Central Laboratory in Zambia: **Removal of:** Protocol Development Committee details, as this can be found in: 15iii.ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT GROUPS & INDIVIDUALS
iii TRIAL SUMMARY	Change of the planned start date and planned end date. **Change from:** **Planned start date** 1 February 2020 **Planned end date** 30 July 2020, or when 120 evaluable patients have been recruited. **To:** **Planned start date** 1 May 2020, or when the first evaluable patient has been recruited. **Planned end date** 1 May 2021, or when 120 evaluable patients have been recruited.
4 TRIAL DESIGN	**Change from:** A prospective, randomised, open label study to be conducted in obstetric units in Pakistan. **To:** A prospective, randomised, open label study to be conducted in obstetric units in Pakistan and Zambia.
5 TRIAL SETTING	**Change from:** Participants will be recruited from obstetric units in Pakistan. **To:** Participants will be recruited from obstetric units in Pakistan and Zambia.
9.4 Data Monitoring Committee (DMC) **15 iii ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT GROUPS & INDIVIDUALS** **Appendix 3**	Addition of the information regarding the Data Monitoring Committee.

Summary of changes between version 1 and 1.1

Protocol Section	Description of change
iv. TRIAL OVERVIEW **7.5 TXA administration and timing of biological samples** **7.9 Summary of trial procedures**	Clarification of the time point T_0 in which participants receive the trial intervention. **Change from:** Timepoint T_0-Give intervention as randomised about 1 hour prior to caesarean section. **To:** Timepoint T_0-Give intervention as randomised about 1 hour **(± 30 min)** prior to caesarean section.
7.1 Screening of potential participants **7.2.1 Information giving**	Clarification of the screening of potential participants. **Change from**: when the woman is admitted for a scheduled CS. **To:** when the woman is admitted for a CS.
7.12.2 Procedure for replacing participants	Clarification of the procedure for replacing participants.
10.3.1 Pharmacokinetic analysis	**Change from:** All participants who receive one dose of TXA and have at least six PK samples obtained after TXA administration to determine maternal plasma concentrations of TXA will be included in the PK data analysis. **To:** All participants who receive the full dose of TXA and did not vomit the oral dose within the first hour and have at least six PK samples obtained after TXA administration to determine maternal plasma concentrations of TXA will be included in the PK data analysis.

18 APPENDICES

18.1 Appendix 1 - Participant Information Sheet and Informed Consent Form

[HOSPITAL CONTACT DETAILS]
Name of PI
Name of Hospital
Hospital address
Contact phone number

A randomised controlled trial to assess the pharmacokinetics and pharmacodynamics of intramuscular, intravenous and oral administration of tranexamic acid in women giving birth by caesarean section

STUDY INFORMATION FOR PARTICIPANTS

We invite you to take part in a research study called WOMAN-PharmacoTXA

- Before you decide to take part or not, we would like you to know why the study is being done and what it will involve.
- Please read this information. You can talk to others about the study if you wish.
- You can ask the doctor or midwife looking after you as many questions about the study as you like before deciding to take part or not.
- It is up to you to decide to take part in this study or not. If you choose not to take part, your doctors and midwives will give you the usual care given at this hospital.

Contents

1. What is the study for?

Some women experience heavy bleeding during and after having a caesarean section (C- section) birth. We already know that giving a drug called tranexamic acid or TXA into the vein of women who develop heavy bleeding after childbirth can save their lives. However, the treatment has to be given really early and no later than 3 hours after giving birth. It would be better if we could stop women from having a large bleed in the first place. We want to find out if giving tranexamic acid to women who are having a C-section stops them from bleeding too much, especially those women who are at risk of having a large bleed.

We also want to know which way of giving TXA works. Usually TXA is given by injection in the vein, this needs to be done by a qualified medical person who may not be available especially when women give birth at home or in small clinics.

TXA can also be given as an injection into muscles or as a drink, these ways of giving the drug may be easier and quicker. Our aim is to see if giving TXA in a drink or by injecting in the muscle can be absorbed by the body and work as well as when it is given in the vein, this information will help women at risk of bleeding in the future.

2. Why are you asking me to take part?

We are asking you to take part because you are expected to give birth by a caesarean section and you are at a high risk of heavy bleeding afterwards.

We are giving this information to you and asking you to take part. If you agree the study team at this hospital can include you in the study.

You will not be able to take part if:

- You are less than 18 years old
- You will be giving birth vaginally
- Your C-section has to be done urgently (less than 1 hour after your admission to hospital).
- You are allergic to the study drug
- You develop severe bleeding before the caesarean section
- You have received tranexamic acid within 48 before the caesarean section
- Your kidneys are not functioning properly
- You have any medical condition which makes you bleed a lot

About 120 women will be taking part in this study. It is up to you to decide if you wish to take part or not.

3. What will happen if I take part?

Taking part in the study will not change the usual care given to women having a C-section at your hospital.

- We will ask you to fill in a form to say that you are willing to take part.
- We will ask you some questions about your health, measure your height and weight, take your blood pressure, heart rate and your breathing rate.
- We will take a small sample of blood from your vein to do a blood test to tell us about your blood clotting, how well your kidneys are working and if you are anaemic or not. This will be

taken from the needle which is put into your vein to prepare you for surgery so there will be no extra needles for this.

- About one hour before your C-Section we will do a small finger prick blood test.

We will then choose one of four ways to treat you. The treatment you will get is decided is by a computer and the doctors cannot change this. They will not know in advance what you will receive. Each person has an equal chance of receiving any one of the following:

1. an injection of tranexamic acid in a vein
2. two injections of tranexamic acid in different muscles
3. tranexamic acid in a drink
4. no tranexamic acid.

We will then repeat the finger prick blood tests and blood samples from the needle in your vein. We will also check your blood pressure, heart rate and breathing rate, how much blood you have lost and if you have any problems from the treatment. We will record the checks which are done on all babies at birth called the APGAR score. Immediately after the birth of your baby, once the umbilical cord is clamped, we will collect a small blood from the umbilical cord. All babies have a routine blood test done soon after birth using a small prick on the heel. At the same time this is done, we will take a small blood sample from your baby. We will also check you and your baby for any medical problems while you are in hospital. Also, if you received your treatment by injection into your muscles, we will check for any pain, bruising or any other problems.
You can see in the table below how often we will need carry out these checks.

Time after TXA or no TXA	**Finger prick test**	**Blood test from needle in vein**	**Heart rate, Blood pressure, breathing rate**	**Blood loss**	**Collect any Information about any treatments you receive**	**Check for any medical problems you have**	**Check if you have any problems if you had the injection into your muscles**	**Check for any medical problems your baby may have**
15 minutes	*x*		*x*	*x*	*x*	*x*	*x*	*x*
30 minutes	*x*		*x*	*x*	*x*	*x*	*x*	*x*
2 hours	x		x	x	x	x	x	x
4 hours	x	x	x	x	x	x	x	x
8 hours	x	x	x	x	x	x	x	x
12 hours	x	x	x	x	x	x	x	x
24 hours	x	x	x	x	x	x	x	x
Every day to discharge or day 7			x			x	x	x

4. How long will I be in this study?

You will be in the study until you leave hospital, or for seven days after you had your baby, whichever is sooner. If after leaving hospital and within seven days of giving birth, you or your baby become ill, please let the doctor named on this form know.

5. Will I benefit from taking part in this study?

We do not know if taking part in this study will help you personally or not. What we learn from this study will help doctors care for women at risk of having a large bleed after giving birth in the future. We hope that giving TXA before the caesarean section to women at risk of bleeding a lot, may prevent large bleeds. We hope that if TXA works when it is given in the muscle or drunk in a solution, these may help other women in the future that are in a situation where receiving an injection into a vein is not possible.

6. Could I be harmed by taking part?

Tranexamic acid is not a new drug and it is often used to treat people with other types of bleeding, such as when having an operation or after childbirth. Several studies suggest that it doesn't have any serious side effects. Sometimes it can cause nausea, vomiting, and diarrhoea. If you receive the injection in your muscles there is a small risk of redness, pain, and bruising at the injection sites in your muscles and there is a very rare risk of infection.

Previous studies that administered tranexamic acid to pregnant women did not identify harmful effects for the baby. A very small amount of tranexamic acid can pass into breast milk. Other studies have not found any harmful effects in babies who were breastfed by mothers who were given tranexamic acid. Your doctor will watch you and your baby, and give you the best available care if there are any problems. They will also tell the people running the study if you have any problems.

7. Can I change my mind about taking part?

Yes. You can stop taking part in the study, at any time. You just need to say something like, *"I've decided I don't want to be in this study anymore"*. Your doctor and the hospital staff will still care for you in the usual way. If you have any medical problems after you stop taking part, we ask that you still tell us about them.

8. What happens afterwards?

We will give you a card with the contact details of the study doctor at this hospital. Please keep this card safe. If after you leave hospital you or your baby become ill within seven days of having your baby, please contact the study doctor listed on the card. Also, please show this card to anyone who treats you for any illness.

If you would like to have a copy of the final results of this study, please let the doctor discussing this study with you know and s/he will make sure you receive a copy when the results are published.

9. What information do we keep private?

We will keep all information collected about you and your baby private and stored securely. The only people allowed to look at the information will be the staff who are running the trial at the London Coordinating Centre and the Coordinating Centre in your country [Name], as well as the regulatory authorities who check that the study is being carried out correctly. The London Coordinating Centre

may want to collect or copy some study information which will have your name on it such as the signed Consent Form. These will be destroyed or your personal details removed immediately after use.

We will publish the study results in medical journals so that other doctors and midwives can learn from them. We will not include your personal information in any study reports, so you will not be able to be identified. The study team may share data from the study with other researchers and the public, but your personal information will not be included.

10. What will happen to your blood samples?

Your finger prick blood samples will be prepared and then shipped securely via a specialised courier service to a Laboratory at the University Versailles Saint Quentin (France). They will measure the quantity of TXA in the samples. Our staff at the laboratory will not be able to identify you. All the blood samples taken from your vein will be tested at a local Laboratory in your country [Name]. Your samples will be destroyed safely after they have been analysed or latest at the end of the study.

11. Who is doing this study? Who can I contact about any questions, or if I have a problem?

The study is run by a team of researchers at the London School of Hygiene & Tropical Medicine (University of London) in the United Kingdom.

If you have any questions or concerns about the study, you should ask to speak with the study team who will do their best to answer your questions. You can contact the doctor in charge of the trial at this hospital at:

Name	
Address:	
Telephone:	
Email:	

If you wish to complain formally, you can do this through the hospital's complaints procedure. Please ask the study doctors or midwives for details.

12. Who has reviewed the study?

To look after your interests, this study has been carefully checked by an independent group of people called a Research Ethics Committee. They agreed that it is okay for us to do this study. This study has been reviewed and has been given a favourable ethical opinion by a Research Ethics Committee called:

13. What if there is a problem?

If something goes wrong during the study, the London School of Hygiene & Tropical Medicine would be responsible for claims for any non-negligent harm.

14. What else do I need to know?

If you/the patient are injured as a result of being in this study, you should contact the study doctor. In the event of a bodily injury or illness directly resulting from the study product, the sponsor will pay for reasonable and necessary treatment. The sponsor is not responsible for medical expenses due to pre-existing medical conditions, any underlying diseases, any ongoing treatment process, your negligence or wilful misconduct, the negligence or wilful misconduct of the study doctor or the study site or any third parties. You do not lose any of your legal rights to seek compensation by signing this form.

- The study is organised by London School of Hygiene and Tropical Medicine (LSHTM, University of London, UK) and funded by the Wellcome Trust (UK) and the Bill and Melinda Gates Foundation (USA). None of these institutions are the makers of tranexamic acid.
- If you agree to take part, you will sign a separate consent form. We will give you a copy of your consent form and this information sheet.
- The study treatment is free. It will not cost you any money to take part in this study.
- If you return to hospital for any medical problem associated with the study, we will pay your travel costs.

CONSENT FORM

WOMAN PHARMACO-TXA TRIAL

TITLE OF RESEARCH	A randomised controlled trial to assess the pharmacokinetics and pharmacodynamics of intramuscular, intravenous and oral administration of tranexamic acid in women giving birth by caesarean section.		
VERSION NUMBER	1.1	**VERSION DATE**	3 MARCH 2020
SITE ID NUMBER		**NAME OF RESEARCHER**	
PARTICIPANT SCREENING ID NUMBER			

STATEMENT OF PERSON GIVING CONSENT:

1. I confirm that I have read/have had read to me the information sheet for the above study and it was in a language I understand.
2. I have discussed with the doctor to my satisfaction and I have had the opportunity to ask questions.
3. I understand that my participation is voluntary. I have been given enough information about the research study to judge that I want to take part in it.
4. I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
5. I understand that I will be given a copy of this consent form and the additional information sheet to keep for myself.
6. I understand that sections of my medical notes and those of my baby/ies may be looked at by responsible individuals involved in the study. I give permission for these individuals to have access to these records.
7. I understand that my data (with all personal information removed) will be made freely available for the public.
8. I understand that the blood samples collected from me will be sent abroad, to France, for analysis and not stored for future research. The samples will not be labelled with any personal information, only a study identification number will be used.
9. I give permission for a copy of this consent form, which contains my personal information, to be made available to the Trial Coordinating Centre in London for monitoring purposes only.
10. I agree to take part in the above study, the WOMAN PHARMACO-TXA trial.

_____	_____	_____
Name of woman	Date	Signature / Thumbprint or other mark (if unable to sign)
_____	_____	_____
Name of witness	Date	Signature

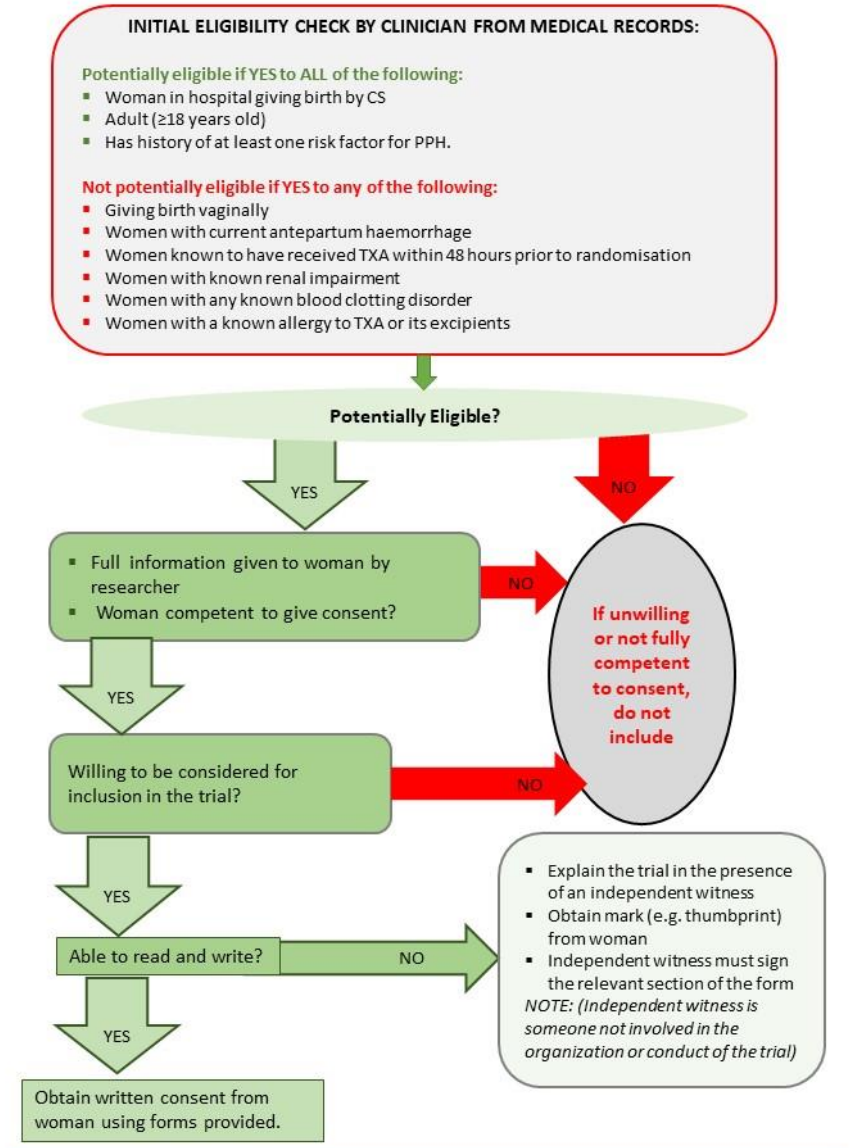
(A witness not associated with the trial is needed if a patient cannot read or write)

STATEMENT OF PERSON OBTAINING INFORMED CONSENT:

I have fully explained this research to this participant and have given sufficient information, including about risks and benefits, to make an informed decision.

_____	_____	_____
Name	Date	Signature

18.2 Appendix 2 - Consent procedure overview



NOTE: In all cases:

- Researcher/Clinician obtaining consent must also sign the relevant section of the consent form
- File original signed consent form in Investigator's Site File
- Give copy of signed form to woman
- File one signed copy in the woman's medical notes
- Document consent process used in woman's medical notes

18.3 Appendix 3 – Data Monitoring Committee

Membership:

NAME	AFFILIATION	EXPERTISE
Folasade Adenike Bello (Chair)	Department of Obstetrics and Gynaecology Faculty of Clinical Sciences College of Medicine University of Ibadan Nigeria	Obstetrician and Gynaecologist. Clinical trial and Public Health expert.
Humaira Bilqis	Department of Obstetrics and Gynaecology Rawalpindi Medical University Rawalpindi Pakistan	Obstetrician and Gynaecologist. Clinical trial expert.
Andrew Kumwenda	Department of Obstetrics and Gynaecology School of Medicine University of Zambia Lusaka Zambia	Obstetrician and Gynaecologist. Public Health expert.